8EHQ-0601-14931

MR 48718

degussa.

Management Services

June 4, 2001

Document Processing Center (TS-790)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

ATTN: Section 8 (e) Coordinator

RE: Product Name: N,N-bis(20hydroxypropyl)-p-toluidine
CAS Registry No. 38668-48-3
CAS Registry Name: 2-Propanol, 1,1'-[4-methylphenyl)imino]bis-

Dear Sir or Madam:

Degussa Corporation has received from Röhm GmbH, the enclosed report on "Acute oral toxicity study in the rat (acute toxic class method)." This is a follow up to the TSCA 8(e) submission made May 22, 2001 on the subject product.

Pursuant to Section 8 (e) of the Toxic Substances Control Act, Degussa Corporation provides this information to EPA.

Sincerely,

Kisha Pippins

Kisha Pippins
Product Safety Specialist

cc: R. Brazicki

Contain NO CBI

RTC

RESEARCH TOXICOLOGY CENTRE - ROMA

N,N-bis(2-hydroxypropyl)-p-toluidine
ACUTE ORAL TOXICITY STUDY IN THE RAT
(ACUTE TOXIC CLASS METHOD)

FINAL REPORT

RTC Study Number: 8562

RTC Report Number: 8562/T/137/2001

Sponsor:
RÖHM GmbH & Co. KG
Kirschenallee
D-64293 Darmstadt
Germany

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Partita IVA: 00920611001

RTC Report Number: 8562/T/137/2001

COMPLIANCE STATEMENT

We, the undersigned, hereby declare that the following report constitutes a true and faithful account of the procedures adopted, and the results obtained in the performance of this study. The aspects of the study conducted by Research Toxicology Centre S.p.A. were performed in accordance with:

A. Commission Directive 1999/11/EC of 8 March 1999 adapting to technical progress the principles of good laboratory practice as specified in Council Directive 87/18/EEC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (adoption of the *"OECD principles on Good Laboratory Practice – as revised in 1997"*) and subsequent revisions.

B. Decreto Legislativo 27 gennaio 1992, n. 120 published in the Gazzetta Ufficiale della Repubblica Italiana 18 Febbraio 1992 (adoption of the Commission Directive of 18 December 1989 adapting to technical progress the Annex to Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (90/18/EEC)) and subsequent revisions.

M. A. Antonelli, Biol. D., Spec. Tox.
(Study Director): Date : 21.05.01

J. Brightwell, Ph.D.
(Scientific Director): Date : 21.05.2001

RTC Report Number: 8562/T/137/2001

QUALITY ASSURANCE STATEMENT

(Relevant to those aspects of the study conducted by Research Toxicology Centre S.p.A.)

Study phases monitored by RTC's QAU according to current relevant Standard Operating Procedures	Quality Assurance Inspections (Day Month Year)		
	Inspection	Report to Study Director	Report to Company Management
PROTOCOL CHECK	05.03.2001	05.03.2001	05.03.2001
PROCESS-BASED INSPECTIONS			
Allocation	06.02.2001	-	24.04.2001
Dose preparation	02.03.2001	-	16.03.2001
Body weight	20.03.2001	-	17.04.2001
Dosing (oral)	07.02.2001	-	22.02.2001
Clinical observations	14.02.2001	-	16.03.2001
Despatch to necropsy	10.04.2001	-	17.04.2001
Necropsy	26.01.2001	-	01.02.2001
Other routine inspections of a procedural nature were carried out on activities not directly related to this type of study. The relevant documentation is kept on file although specific inspection dates are not reported here.			
FINAL REPORT Review of this report by RTC's QAU found the reported methods and procedures to describe those used and the results to constitute an accurate representation of the recorded raw data.			Review completed 18/05/01

M. Brunetti, Biol.D.
(Head of Quality Assurance)

18/05/01
Date

Contents

Tables

1. SUMMARY

The acute toxicity of N,N-bis(2-hydroxypropyl)-p-toluidine was investigated following administration of a single oral dose to the rat.

A single group of 3 male animals was dosed at a level of 2000 mg/kg. All animals showed convulsions approximately 1 minute after dosing just prior to death.

Three male animals were then dosed at a level of 200 mg/kg and observed for a period of 14 days. Two animals showed convulsions and pronation approximately 5 minutes after dosing and died within 1 hour post-dose observation period. Piloerection and yellow staining in litter tray were observed in the surviving animal.

Three male animals were then dosed at a level of 25 mg/kg and observed for a period of 14 days. No mortality occurred and no clinical signs were observed following treatment. A group of three females was finally dosed at 25 mg/kg and observed for a period of 14 days. No mortality occurred and no clinical signs were observed following treatment.

Animals were killed at the end of the observation period. All animals were subjected to necropsy examination.

Changes in body weight observed in treated animals were not remarkable.

An abnormal content was found in the stomach and in the jejunum of the early decedent males. A skin/fur staining around the perioral/perinasal region was also seen in a number of these animals. No abnormalities were found on necropsy of animals performed on termination of the study.

These results indicate that the test item, N,N-bis(2-hydroxypropyl)-p-toluidine, has a severe toxic effect in the rat following oral administration of a single dose at a level of 2000 and 200 mg/kg. The observed mortality pattern demonstrates the LD50 to be less than 200 mg/kg and greater than 25 mg/kg body weight.

European Directives concerning the classification, packaging and labelling of dangerous substances would suggest the following:-

Classification : Required
Symbol : T
R phrase : R25 – Toxic if swallowed

2. INTRODUCTION

The purpose of this study was to assess the acute toxicity of the substance following oral administration of a single dose to the rat. This allowed hazard assessment of the substance as required by European Directives concerning the classification, packaging and labelling of dangerous substances (67/548/EEC and subsequent revisions).

The procedures being used were designed to meet the requirements of the test for acute oral toxicity described in OECD guideline Number 423, adopted on 22nd March 1996. Methods were in agreement with those of B.1 *tris* detailed in Directive 96/54/EEC. The rat was used, being a species indicated in the guidelines for this test. The route of administration is a potential route of exposure during manufacturing, handling or use of the substance.

The study was carried out at: Research Toxicology Centre S.p.A.
Via Tito Speri, 12
00040 Pomezia (Roma)
Italy

On behalf of: RÖHM GmbH & Co. KG
Kirschenallee
D-64293 Darmstadt
Germany

The study started on 16th February 2001 with signing of the protocol by the Study Director. The experimental work described in this report started on 1st March 2001 with allocation of animals to the first phase of the study and ended on 10th April 2001 with termination of the last phase of the study. The study was completed on the date shown against the Study Director signature at the front of this report.

3. TEST ITEM

Details of the test item received at RTC are as follows:

Name	: N,N-bis(2-hydroxypropyl)-p-toluidine
Alternative name	: Diisopropanol-para-toluidine
CAS no.	: 38668-48-3
Lot or Batch Number	: Z011020622
Expiry date	: -
Received from	: RÖHM GmbH & Co. KG
Date received	: 23rd February 2001
Amount received	: 50 grams
Description	: Solid, whitish scales
Container	: Colourless glass bottle
Storage at RTC	: Ambient conditions
RTC reference number	: 5203

Detailed characterisation of the substance was not undertaken at the testing facility. The determination of the identity, strength, purity, composition, stability and method of synthesis and/or derivation of the substance was the responsibility of the Sponsor. An aliquot of the supplied substance was taken and will be retained within the RTC archives for a period of 10 years prior to disposal.

The test item was formulated for dosing by dissolution/suspension in corn oil to give concentrations of 200, 20 and 2.5 mg/ml.

During handling of the substance, precautions were taken to reduce possible operator exposure. This included, but was not limited to, use of a face mask, eye protection and the wearing of gloves.

4. METHODS

Any deviations from the protocol are detailed within the text of the report. No deviations occurred which were considered to have compromised the purpose or conduct of the study.

Dated and signed records were made of all activities relating to the day by day conduct and maintenance of the study.

4.1 Animal management

4.1.1 Animal supply

Healthy rats of the Hsd: Sprague Dawley SD strain were ordered from Harlan Nossan S.r.l., Correzzana (MI), Italy and were supplied by Harlan Italy S.r.l., 33049 San Pietro al Natisone (UD), Italy. Animals were ordered weighing 120 to 150 grams and aged approximately 5 to 6 weeks with female animals nulliparous and non-pregnant. Animals appeared to be in an acceptable condition following arrival, in batches for the different phases of the study, on 2nd February and on 2nd March 2001. A pre-dose acclimatisation period of at least 5 days was allowed.

4.1.2 Animal husbandry

Animals included in the study were housed, in groups of 3 animals of the same sex, in polycarbonate cages measuring 59x20x39 cm and equipped with a stainless steel mesh lid and floor. Cages were suspended over trays holding an absorbent material which was inspected daily and changed as necessary. Throughout the study each cage was identified by a colour coded label recording the study number, animal number and the details of treatment. This colour coding matched the corresponding colour coded formulation container.

Animal room controls were set to maintain temperature within the range of 20 to 24°C and relative humidity within the range of 40 to 70%. Actual conditions were recorded.

The room was lit by fluorescent tubes controlled to give an artificial cycle of 12 hours light and 12 hours dark each day.

4.1.3 Water and diet

Animals were offered drinking water supplied to each cage via a water bottle and a commercially available laboratory rodent diet (Altromin MT, Altromin, D-32770, Lage, Postfach 1120, Germany) ad libitum throughout the study except for an overnight fast prior to dosing and a period of approximately 4 hours after dosing.

There was no information to indicate that any component present in the drinking water or diet was at a level likely to interfere with the purpose or conduct of the study.

4.2 Experimental design

A single group of 3 males was initially allocated to the study and treated at a level of 2000 mg/kg. Mortality occurred at this dose level and an additional group of 3 males was dosed at 200 mg/kg. Since mortality occurred at this dose level, additional groups of 3 males and 3 females were dosed at 25 mg/kg.

4.2.1 Selection and allocation

The required number of animals for the study was selected from available stock and allocated to treatment groups. Individuals were permanently identified on arrival by a combination of ear notch (units) and tattoo and not on inclusion in the study by random numbers as indicated in the study protocol. This is a deviation from the protocol. Males were identified by even numbers and females by odd numbers.

A total of 3 groups were allocated to the study as follows:-

Dose level (mg/kg)	Animal number	
	Males	Females
2000	14, 16, 18	-
200	42, 44, 46	-
25	64, 66, 68	63, 65, 67

Food was removed from cages overnight prior to dosing.

4.2.2 Dosing

The next day, (Day 1 of the study), the amount of supplied test item to be administered was calculated for each fasted animal according to body weight. This was administered, by gavage at a dose volume of 10 ml/kg, using a rubber catheter attached to a syringe of suitable capacity.

Food was made available approximately 4 hours after dosing.

4.2.3 Mortality and morbidity

Throughout the study all animals were checked twice daily.

4.2.4 Clinical signs

Animals were observed for clinical signs immediately upon dosing, approximately 1, 2 and 4 hours after dosing and daily thereafter for a total of 14 days.

4.2.5 Body weight

All animals were weighed at allocation to the study (Day -1), immediately prior to dosing (Day 1) and on Days 8 and 15.

4.2.6 Termination

All surviving animals were killed on Day 15 by carbon dioxide narcosis.

Animals were subjected to a gross necropsy examination for both external and internal abnormalities. The cranial, thoracic and abdominal cavities were opened to allow examination of their contents. Larger organs were sectioned. Both the stomach and representative sections of the gastro-intestinal tract were opened for examination of the mucosal surfaces.

4.3 Classification

The results obtained were used to indicate if classification of the test item is necessary according to the requirements of European Directives concerning the classification, packaging and labelling of dangerous preparations (67/548/EEC and subsequent revisions).

4.4 Archives

The raw data and documentation generated during the course of this study will be retained at RTC for a period of 5 years after which the Sponsor will be contacted for instructions regarding despatch or disposal of the material.

5. RESULTS

5.1 Mortality and Clinical signs (Table 1)

All 3 male animals dosed at 2000 mg/kg showed convulsions approximately 1 minute after dosing just prior to death.

Two of the 3 male animals dosed at 200 mg/kg showed convulsions and pronation approximately 5 minutes after dosing and died within one hour of dosing. Clinical signs observed in the remaining animal were limited to piloerection and yellow staining in the litter tray which were noted on one occasion only. Recovery had occurred by Day 3 of the observation period.

No mortality occurred and no clinical signs were observed in male and female animals dosed at 25 mg/kg.

5.2 Body weight (Table 2)

Changes in body weight observed during the period of the study were within the range expected for this strain and age of animal.

5.3 Necropsy (Table 3)

An abnormal content (yellow or pale mucoid or creamy material) was found in the stomach and in the jejunum of the early decedent male animals. A skin/fur staining around the perioral/perinasal region was also seen in a number of these animals.
No abnormalities were found on necropsy of animals at termination of the study.

6. CONCLUSION

The results of this study indicate that the test item, N,N-bis(2-hydroxypropyl)-p-toluidine, has a severe toxic effect in the rat following oral administration of a single dose at a level of 2000 and 200 mg/kg. The observed mortality pattern demonstrates the LD50 to be less than 200 mg/kg and greater than 25 mg/kg body weight.

European Directives concerning the classification, packaging and labelling of dangerous substances would suggest the following:-

Classification : Required
Symbol : T
R phrase : R25 – Toxic if swallowed

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 1 - CLINICAL SIGNS

DOSE LEVEL: 2000 mg/kg

MALES - Number of animals with signs (Number of animals dosed = 3)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	0	-	-	-	-	-	-	-	-	-
Convulsions	3*	-	-	-	-	-	-	-	-	-
MORTALITY	3	-	-	-	-	-	-	-	-	-

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing
* : Approximately 1 minute after dosing

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 1 - Continued

DOSE LEVEL: 200 mg/kg

MALES - Number of animals with signs (Number of animals dosed = 3)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	3	1	1	0	0	1	1	1	1	1
Piloerection	0	0	0	1	0	0	0	0	0	0
Yellow staining - in litter tray	0	0	0	0	1	0	0	0	0	0
Convulsions	2*	0	0	0	0	0	0	0	0	0
Pronation	2*	0	0	0	0	0	0	0	0	0
MORTALITY	0	2	0	0	0	0	0	0	0	0

Sign observed	Day 8	9	10	11	12	13	14	15
No abnormalities detected	1	1	1	1	1	1	1	1
MORTALITY	0	0	0	0	0	0	0	0

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing
* : Approximately 5 minutes after dosing

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 1 - Continued

DOSE LEVEL: 25 mg/kg

MALES - Number of animals with signs (Number of animals dosed = 3)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	3	3	3	3	3	3	3	3	3	3
MORTALITY	0	0	0	0	0	0	0	0	0	0

Sign observed	Day 8	9	10	11	12	13	14	15
No abnormalities detected	3	3	3	3	3	3	3	3
MORTALITY	0	0	0	0	0	0	0	0

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 1 - Continued

DOSE LEVEL: 25 mg/kg

FEMALES - Number of animals with signs (Number of animals dosed = 3)

Sign observed	Day 1 Time 0	1	2	3	Day 2	3	4	5	6	7
No abnormalities detected	3	3	3	3	3	3	3	3	3	3
MORTALITY	0	0	0	0	0	0	0	0	0	0

Sign observed	Day 8	9	10	11	12	13	14	15
No abnormalities detected	3	3	3	3	3	3	3	3
MORTALITY	0	0	0	0	0	0	0	0

KEY Day 1 : Time 0 : At dosing
Time 1 : Approximately 1 hour after dosing
Time 2 : Approximately 2 hours after dosing
Time 3 : Approximately 4 hours after dosing

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 2 - BODY WEIGHT

DOSE LEVEL: 2000 mg/kg

Sex	Animal identity number	Body weight (g) on Day -1	1	8	15	Change in body weight (g) Days 1 - 15
M	14	329	303	-	-	-
A	16	302	274	-	-	-
L	18	337	309	-	-	-
E	Mean	322.7	295.3	N/A	N/A	N/A
S	S.Dev.	18.3	18.7	N/A	N/A	N/A

DOSE LEVEL: 200 mg/kg

Sex	Animal identity number	Body weight (g) on Day -1	1	8	15	Change in body weight Days 1 - 15
M	42	328	307	-	-	-
A	44	340	317	-	-	-
L	46	343	320	364	396	76
E						
S	Mean	337.0	314.7	N/A	N/A	N/A
	S.Dev.	7.9	6.8	N/A	N/A	N/A

KEY : - = Decedent
N/A = Not applicable

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 2 - BODY WEIGHT

DOSE LEVEL: 25 mg/kg

Sex	Animal identity number	Body weight (g) on Day -1	1	8	15	Change in body weight (g) Days 1 - 15
M	64	273	249	317	341	92
A	66	277	252	306	342	90
L	68	262	240	298	329	89
E						
S	Mean	270.7	247.0	307.0	337.3	90.3
	S.Dev.	7.8	6.2	9.5	7.2	1.5
F	63	234	212	259	265	53
E	65	197	178	211	219	41
M	67	212	190	223	225	35
A						
L	Mean	214.3	193.3	231.0	236.3	43.0
E	S.Dev.	18.6	17.2	25.0	25.0	9.2
S						

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 3 - NECROPSY

DOSE LEVEL: 2000 mg/kg

MALES

Animal number	Tissue/ organ	Finding
14		Early decedent.
	External surfaces	Red staining perioral/perinasal region.
	Stomach	Contained a pale creamy material.
16		Early decedent.
	External surfaces	Red staining perioral/perinasal region.
	Stomach	Contained a pale creamy material.
18		Early decedent.
	External surfaces	Red staining perioral/perinasal region.
	Stomach	Contained a pale creamy material.

DOSE LEVEL: 200 mg/kg

MALES

Animal number	Tissue/ organ	Finding
42		Early decedent.
	Jejunum	Contained a yellow mucoid material.
44		Early decedent.
	Jejunum	Contained a yellow mucoid material.
46		Terminal kill. No abnormalities found.

ACUTE ORAL TOXICITY STUDY IN THE RAT

RTC STUDY NUMBER: 8562

TABLE 3 - NECROPSY

DOSE LEVEL: 25 mg/kg

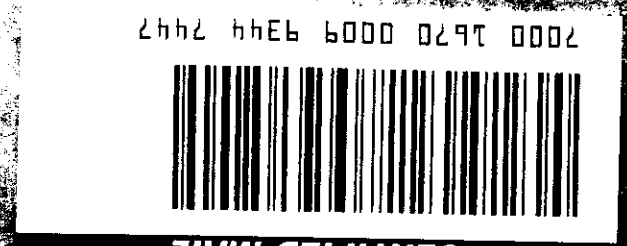
MALES

Animal number	Tissue/ organ	Finding
64		Terminal kill. No abnormalities found.
66		Terminal kill. No abnormalities found.
68		Terminal kill. No abnormalities found.

DOSE LEVEL: 25 mg/kg

FEMALES

Animal number	Tissue/ organ	Finding
63		Terminal kill. No abnormalities found.
65		Terminal kill. No abnormalities found.
67		Terminal kill. No abnormalities found.



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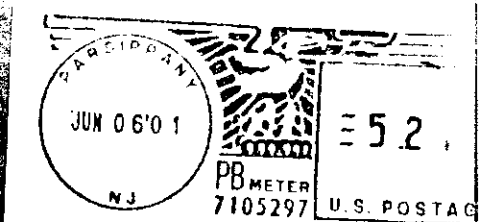

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